IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Turner *et al.*	Group Art Unit: 1652
Application No.:	09/863,824	Examiner: D. M. Ramirez
Filed:	5/23/01	
Title: Novel Human Thrombospondin-Like Proteins and Polynucleotides Encoding the Same		Atty. Docket No. LEX-0181-USA

APPEAL BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

STATUTES

APPEAL BRIEF

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Office Action mailed on December 3, 2003. The Notice of Appeal was timely submitted on March 3, 2003, and was received in the Patent and Trademark Office ("the Office") on March 12, 2003. This Appeal Brief is timely submitted in light of the concurrently filed Petition for an Extension of Time of two months to July 12, 2003, which falls on a Saturday and is therefore extended to to and including July 14, 2003 and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(2) from Appellants' Representatives' deposit account. The Commissioner is also authorized to charge the fee for filing this Appeal Brief (**$160.00**), as required under 37 C.F.R. § 1.17(c), to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

Appellants believe no fees in addition to the fee for filing the Appeal Brief and the fee for the extension of time are due in connection with this Appeal Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, Lexicon Genetics Incorporated, 8800 Technology Forest Place, The Woodlands, Texas, 77381.

II. RELATED APPEALS AND INTERFERENCES

Appellants know of no related appeals or interferences.

III. STATUS OF THE CLAIMS

The present application was filed on May 23, 2001, claiming the benefit of U.S. Provisional

Application Number 60/206,415, which was filed on May 23, 2000, and included original claims 1-5. A Restriction and Election Requirement was issued by the Office on January 11, 2002, separating the original claims into five separate and distinct inventions. In a response to the Restriction Requirement, submitted to the Office on February 11, 2002, Appellants elected with traverse the claims of the Group I invention (original claims 1-3) for prosecution on the merits. Appellants further elected, pursuant to 35 U.S.C. § 121, the species of SEQ ID NO:1 for initial examination on merits.

A First Official Action, was issued on May 14, 2002 ("the First Action") , claims 4-5 were withdrawn under 37 CFR 1.142(b) as being drawn to a non-elected invention, claims 1-3 were rejected to under 35 U.S.C. § 101 as allegedly lacking patentable utility, claims 1-3 were also rejected under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, and claim 2 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In a response to the First Official Action, submitted to the Office on September 16, 2002 ("response to the First Action"), Appellants cancelled claim 1 without prejudice and without disclaimer, claims 4 and 5 were canceled without prejudice and without disclaimer as being drawn to non-elected inventions, claim 2 was amended to further improve its clarity, and new claims 6 and 7 were added to more particularly point out and distinctly claim the invention.

A Second and Final Official Action, was issued on December 3, 2002 (the "Final Action"), in which rejection of claims 2, 3, 6 and 7 was maintained under 35 U.S.C. § 101 as allegedly lacking a patentable utility, rejection of claims 2, 3, 6 and 7 was also maintained under 35 U.S.C. § 112, first paragraph, as one skilled in the art clearly would not know how to use the skilled invention, rejection of claim 2 under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite was also maintained. In a response to the Final Action, submitted on May 5, 2003 ("response to the Final Action"), claim 2 was amended to further improve its clarity and Appellants again addressed the outstanding rejections of claims 2, 3, 6 and 7. An Advisory Action ("the Advisory Action") was mailed on June 3, 2003, maintaining the rejection of claims 2, 3, 6 and 7 under 35 U.S.C. § 101 as allegedly lacking a patentable utility, and the rejection of claims 2, 3, 6 and 7 under 35 U.S.C. § 112, first paragraph, as one skilled in the art clearly would not know how to use the invention. In addition, the rejection of claim 2 under 35 U.S.C. § 112,

second paragraph, as being allegedly indefinite was also maintained. Therefore, claims 2, 3, 6 and 7 are the subject of this appeal. A copy of the appealed claims are included below in the Appendix (Section IX).

IV. STATUS OF THE AMENDMENTS

The amendments revising claims 2 and the abstract were not entered by the Examiner following the response to the Final Action mailed on May 5, 2003. Appellants believe that no additional outstanding amendments exist.

V. SUMMARY OF THE INVENTION

The present invention relates to Appellants' discovery and identification of novel human polynucleotide sequences that encode proteins sharing tissue specificity and structural similarity with human thrombospondin (see, at least, the specification title, page 1, line 11 and lines 23-25; page 2, line 2; page 4, lines 21-28 and page 16, lines 7-12). The presently claimed polynucleotide sequences were compiled from clustered human gene trapped sequences and cDNA products isolated from human skeletal muscle, mammary gland, uterus, and kidney mRNAs. The described sequences share substantial structural similarity with a variety of proteins, including, but not limited to, thrombospondins (via tsp1 repeats) (specification at page 16, lines 7-12 and at page 7, lines 25-31). The specification details a number of uses for the presently claimed polynucleotide sequences, because of their potential medical significance, thrombospondin and semaphorin protein homologs have been subject to considerable scientific scrutiny as evidenced in U.S. Patents Nos. 5,155,038, 5,981,222 and 6,013,781, which are herein incorporated by reference (specification at page 16, lines 14-17). Additional utilities include use as reagents in assays for screening for compounds that can be used as pharmaceutical reagents useful in the therapeutic treatment of mental, biological, or medical disorders and diseases (specification at page 19, lines 5-14). Additional uses include assessing temporal and tissue specific gene expression patterns (specification at page 5, line 4-5 the results of which are described on page 3, lines 11-16), particularly using a high throughput "chip" format (specification at pages 5-7), mapping the sequences to a specific region of a human chromosome and identifying protein encoding regions (specification at page 2, line 28), determining the genomic structure

(specification at page 10, lines 31 through page 11, line 9), intron/exon splice junctions (specification at page 11 line 5) and use of the described polymorphisms (specification at page 16, line 21-31) in diagnostic assays such as forensic analysis, human population biology and paternity determinations.

VI. ISSUES ON APPEAL

1. Do claims 2, 3, 6 and 7 lack a patentable utility?
2. Are claims 2, 3, 6 and 7 unusable by a skilled artisan due to a lack of patentable utility?

VII. GROUPING OF THE CLAIMS

For the purposes of the outstanding rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, the claims will stand or fall together.

VIII. ARGUMENT

A. Do Claims 2, 3, 6 and 7 Lack a Patentable Utility?

The Final Action rejects claims 2, 3, 6 and 7 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by either a specific and substantial utility or a well-established utility. Appellents strongly disagree, as the specification details a number of specific and substantial utilities for the presently claimed polynucleotide sequences, which because of their potential medical significance, thrombospondin and semaphorin protein homologs have been subject to considerable scientific scrutiny as evidenced in U.S. Patents Nos. 5,155,038, 5,981,222 and 6,013,781, which were incorporated by reference (specification at page 16, lines 14-17). Additional utilities include use as reagents in assays for screening for compounds that can be used as pharmaceutical reagents useful in the therapeutic treatment of mental, biological, or medical disorders and diseases (specification at page 19, lines 5-14). Additional uses include assessing temporal and tissue specific gene expression patterns (specification at page 5, line 4-5 the results of which are described on page 3, lines 11-16), particularly using a high throughput "chip"

format (specification at pages 5-7), mapping the sequences to a specific region of a human chromosome and identifying protein encoding regions (specification at page 2, line 28), determining the genomic structure (specification at page 10, lines 31 through page 11, line 9), intron/exon splice junctions (specification at page 11 line 5) and use of the described polymorphisms (specification at page 16, line 21-31) in diagnostic assays such as forensic analysis, human population biology and paternity determinations.

In particular the present invention has a number of substantial and credible utilities, not the least of which relates to polymorphisms identified in the sequences of the present invention described in the specification at page at page 16, line 21-31. For example, the A-G transition that can occur at nucleotide position number 364, of SEQ ID NO:1 and the A-or-T transversion that can occur at nucleotide position number 365 of SEQ ID NO:1 that can give rise to either a asparagine or valine at corresponding amino acid position 122 of SEQ ID NO:2, and an A-or-G transition polymorphism at nucleotide position 535 of, for example, SEQ ID NO:1 which can give rise to a lysine or a glutamic at corresponding amino acid position 179 of, for example, SEQ ID NO:2. These polymorphisms provide significant and specific utility as taught in the specification. Such polymorphisms have significant and specific utility in, *intra alia*, the fields of forensic science, human population biology and in the resolution of paternity issues. Such polymorphisms can also be used as specific markers useful, for example, in identifying human remains, determining human group migration patterns by identifying descendants of a specific group and in addition clearly the polymorphism of the present invention has significant and specific utility in resolving issues of paternity. Further, Applicants submit that these utilities are not only credible, but well established and known to those of skill in the art. As such polymorphisms are the basis for forensic analysis, paternity identification and population biology studies, which are undoubtedly "real world" utilities, the present sequences must in themselves be useful. It is important to note that the presence of more useful polymorphic markers for such analysis would not mean that the present sequences lack utility.

Appellants submit that the presently described polymorphism is useful in forensic analysis **exactly as it was described in the specification as originally filed**. Individual members of a population can be distinguished based on the presence or absence of the described polymorphism, and thus, these sequences are useful without "additional research". Simply because the use of this polymorphic marker

will necessarily provide additional information on the percentage of particular subpopulations that contain this polymorphic marker does not mean that "additional research" is needed in order for this marker as it is presently described in the instant specification to be of use to forensic science. Thus, the Examiner's position does not support the alleged lack of utility.

This is also not a case of a potential utility. As stated above, using the presently described polymorphic marker as described in the specification as originally field will definitely distinguish members of a population from one another. In the worst case scenario, this marker is useful to distinguish 50% of the population (in other words, the marker being present in half of the population). The ability to eliminate 50% of the population from a forensic analysis **clearly** is a real world, practical utility. Appellants fail to understand how, given the widespread and daily use of forensic analysis to distinguish individuals, the use of a polymorphic marker in forensic analysis is not a "substantial" use. With regard to the allegation that the use of the presently described polymorphism in forensic analysis is not a "specific" use, as set forth in the Response to the Final Action, Appellants submit that this is improper on a number of different grounds. First, and most importantly, the Final Action seems to be confusing the requirements of a **specific** utility with a **unique** utility. The fact that other polymorphic markers have been identified in other genetic loci does not mean that Appellants' identification of a polymorphic marker in SEQ ID NO:1 is not specific. As clearly stated by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Just because other polymorphic sequences from the human genome have been described does not mean that the use of the presently described polymorphic markers for forensic analysis is not a specific utility. The requirement for a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with the requirement for a **unique** utility, which is clearly an improper standard. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human

diseases, just to name a few particular examples, because examples of each of these have already been described and patented. However, only the briefest perusal of any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Second, Appellants submit that the asserted forensic utility is specific because it cannot be applied to just any nucleic acid. In fact, the basis for forensic analysis is the fact that such a polymorphic marker is **not** present in all other nucleic acids, but in fact specific and unique to only a certain subset of the population. As such, the presently described polymorphic marker clearly has a specific utility, and therefore the presently claimed invention must meet the requirements for utility under 35 U.S.C. § 101.

In the Final Action and the Advisory Action, the Examiner gave several reasons for the alleged lack of utility. For example, the Final Action on page 3 indicates that the specification discloses no function for the disclosed protein. Appellants stress that "a claim need not 'describe' the invention, such description being the role of the disclosure". *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986) and it is well established that "an inventor is not required to understand the theory of how his invention works". *Micro Motion, Inc. v. Exac Corp.*, 16 USPQ2d 1001, 1013 (Cal. 1990). However, in contradiction, the Actions later made reference to Appellants assertions that the sequences of the present invention encode a thrombospondin. The Advisory Action notes (on page 4, lines 10-15) that as thrombospondins belong to a family of at least 5 members in vertebrates that even if the sequences of the present invention do encode a thrombospondin, the claimed polynucleotides lack specific utility.

In support of this position the Advisory Action cites publications that disclose several examples regarding the unpredictability of assigning function based on structure as a small structural changes can lead to changes in function, however none of these examples are in fact thrombospondins and thus none are direct evidence in the present case. The Advisory Action cites Witkowski *et al.* (Biochemistry 38: 11643-11650, 1999), Van de Loo *et al.* (Proc. Natl. Acad. Sci. USA *92*:6743-6747, 1995), Seffernick *et al*

(J. Bact. 2001, *183*:2405-2410) and Broun *et al.* (Science *282*:1315-1317, 1998) as teaching that prediction of function based on structural homology is unpredictable. These articles are merely examples of a small number of spurious publications that call into doubt the usefulness of function based on shared structure and domains and bioinformatic predictions and that the PTO has repeatedly attempted to use as a basis to deny the utility of nucleic acid sequences. However, without going into the merits (or lack thereof) of all of the cited articles, Appellants point out that the lack of 100% unanimous agreement on the usefulness of shared structure and domains and bioinformatic prediction (there is after all a flat earth society, yet it is generally accepted that the earth is not flat) does not indicate that the claimed nucleic acid sequence lacks a substantial and specific utility. Appellants respectfully point out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be **believable**. Appellants submit that the overwhelming majority of those of skill in the relevant art would **believe** bioinformatic prediction to be a powerful and useful tool, as evidenced by hundreds if not thousands of journal articles.

Rather, the question of utility is a straightforward one. As set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for

any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art.

In re Angstadt and Griffin, supra; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The Final and Advisory Actions discount Appellants' assertion regarding the use of the presently claimed polynucleotides on DNA gene chips, based on the position that such a use would allegedly be generic. Further, these Actions seem to be requiring Appellants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Appellants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. As set forth in Appellants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Clearly, the claimed sequences provide a specific marker of the gene and provide a unique identifier of the corresponding gene in the human genome. Such specific markers are targets for discovering drugs that are associated with human disease, such as cancer. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details at least on page 8, line 20 through page10, line 27. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, exemplified by U.S. Patent Nos. 5,445,934 (**Exhibit A**), 5,556,752 (**Exhibit B**), 5,744,305 (**Exhibit C**), as well as more recently issued U.S. Patent Nos. 5,837,832 (**Exhibit D**), 6,156,501 (**Exhibit E**) and 6,261,776 (**Exhibit F**).

The Board is further requested to consider that, given the huge expense of the drug discovery process, even negative information has great "real world" practical utility. Knowing that a given gene is not expressed in medically relevant tissue provides an informative finding of great value to industry by allowing for the more efficient deployment of expensive drug discovery resources. Such practical considerations are equally applicable to the scientific community in general, in that time and resources

are not wasted chasing what are essentially scientific dead-ends (from the perspective of medical relevance). Clearly, compositions that enhance the utility of such DNA gene chips, such as the presently claimed sequences, must in themselves be useful.

Additionally, only a small percentage of the genome (2-4%) actually encodes exons, which in turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications. This further discounts the Examiner's position that such uses are "generic". The present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value that it was acquired by large pharmaceutical company, Merck & Co., for substantial sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304; **Exhibit G**). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153; **Exhibit H**). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible

(worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the specific utility the present nucleotide sequence has in determining the genomic structure of the corresponding human chromosome (specification at page 14, lines 9-10) , for example mapping the protein encoding regions as described in the specification (page 3, line 26-29) and evidenced below. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequence. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.,* showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* defines that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Appellants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence supporting the Appellants' position, the Board is requested to review, for example, section 3 of Venter

et al. (*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

The Advisory Action states (page 6, line 5-7) that "while it is agreed that the claimed polynucleotides can be used to detect the specific locus which contains the corresponding gene, any polynucleotide encoding a gene product can be used to identify its corresponding locus." Thus, apparently the Examiner recognizes the specificity of this ability, as each gene can specifically be used to detect the specific locus which contains the corresponding gene (but not another). However the Examiner does not appear to recognize the value of this specific and substantial utility for, among others, identifying protein encoding regions.

The Advisory Action also states (page 6, line 10) a concern that no evidence was found in the specification that indicated that SEQ ID NO:1 is indeed an mRNA transcript. Appellants respectfully disagree, as the specification (page 3, lines 10 -18) clearly identifies the expression pattern of the sequences of the present invention as being expressed in, *inter alia,* human cell lines, human brain, fetal brain, pituitary, cerebellum, spinal cord, thymus, spleen, trachea, kidney, liver, thyroid, adrenal gland, salivary gland, heart, uterus, stomach, small intestine, placenta, mammary gland, adipose, skin, esophagus, cervix, pericardium, fetal lung, and gene trapped human cells . As this information is obtained by "Northern" analysis, thus clearly the sequences of the present invention encode selectively expressed mRNA transcripts and thus they represent biologically validated information.

As still further evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided as Exhibit C in Appellants response to the Final Action.(**Exhibit I**). This was the result of a sequence comparison using SEQ ID NO:1 of the present invention and overlaying it to the identified human genomic sequence. By doing this one is able to identify the portions of the genome that encode the present invention. If these regions of the genome are non-contiguous, this is indicative of individual exons. In response to the Advisory

Actions concern as to how intron/exon splice junctions are determined using the sequences of the present invention (page 6, last paragraph), the end of an expressed exon and the non-expressed genomic sequence identifies a intron/exon splice junction. The results of such an analysis indicates that the sequence of the present invention is encoded by more than 7 exons spread non-contiguously along a region of human chromosome 20, at approximately 20q12, which are contained within partially overlapping clones, AL133463.16 and AL050320.19. Thus clearly one would not simply be able to identify the more than 7 protein encoding exons that make up the sequence of the present intention, as they are non-contiguous, from within the large genomic sequence. Nor, would one be able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were.

In the Advisory Action, the Examiner acknowledges Appellants submission of this information (page 6, last paragraph) but again as the Examiner is recognizes no evidence in the specification that indicated that SEQ ID NO:1 is indeed an actual transcript of a gene, the value of the information provided in the exhibit is not recognized. However, as stated above, as the sequences of the present invention were shown to be expressed in some tissues but not others by "Northern" analysis, clearly the sequences of the present invention encode expressed mRNA transcripts that are expressed in some tissues but not in others. Therefore, this evidence supports Appellants assertions that these sequences represent biologically validated, expressed transcripts and that they provide specific and substantial utility for chromosome and genome mapping, and the identification of protein encoding regions of the genome as well as intron/exon splice junctions, as discussed in the previous paragraph.

Finally, with regards to the issue of due process, while Appellants are well aware that each application is examined on its own merits and of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35

U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Board is invited to review U.S. Patent Nos. 5,817,479 (**Exhibit J**), 5,654,173 (**Exhibit K**), and 5,552,281 (**Exhibit L**; each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (**Exhibit M**; which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VIII(B), below), Appellants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Appellants agree that each application is examined on its own merits, Appellants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Given the rapid pace of development in the biotechnology arts, it is difficult for the Appellants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Appellants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Thus, holding Appellants to a different standard of utility is both arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Appellants submit that the rejection of claims 2, 3, 6,and 7 under 35 U.S.C. § 101 must be overruled.

B. Are Claims 2, 3, 6 and 7 Unusable Due to a Lack of Patentable Utility?

The Final Action next rejects claims 2, 3, 6,and 7 under 35 U.S.C. § 112, first paragraph, since

allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility.

The arguments detailed above in **Section VIII(A)** concerning the utility of the presently claimed sequences are incorporated herein by reference. As the Federal Circuit and its predecessor have determined that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph, have the same basis, specifically the disclosure of a credible utility (*In re Brana*, *supra*; *In re Jolles*, 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971)), Appellants submit that as claims 2, 3, 6 and 7 have been shown to have "a specific, substantial, and credible utility", as detailed in **Section VIII(A)** above, the present rejection of claims 2, 3, 6 and 7 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 2, 3, 6,and 7 under 35 U.S.C. § 112, first paragraph, must be overruled.

IX. APPENDIX

The claims involved in this appeal are as follows:

1.(cancelled) An isolated nucleic acid molecule comprising at a nucleotide sequence encoding an amino acid sequence drawn from the group consisting of SEQ ID NOS: 2, 4 and 6.

2.(twice amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 2; and

(b) hybridizes under highly stringent conditions with wash conditions of 0.1xSSC/0.1%SDS at 68°C to the nucleotide sequence molecule of SEQ ID NO: 1 or the complete complement thereof.

3. (original) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:2.

4.(cancelled) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:4.

5.(cancelled) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:6.

6.(previously added) An expression vector comprising a nucleic acid sequence of Claim 3.

7.(previously added) A cell comprising the expression vector of Claim 6.

X. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 2, 3, 6 and 7 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

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